REMARKS

Claims 11-15, 18-20, 33-44 and 50-60 are pending in the present application. Claims 1-10, 16, 17, 21-32, and 45-49 have been canceled without prejudice or disclaimer.

Claims 11, 12, and 18 have been amended to add the phrase "wherein the microsphere does not comprise an enteric coating." Support for this amendment is found at page 3 in the first paragraph of the Description of the Invention. No new matter has been added.

In view of the following, further and favorable consideration is respectfully requested.

1. Rejection of claims 11-15, 18-20, 33-43 and 48-60 under 35 U.S.C. §103(a)

The Official Action states that claims 11-15, 18-20, 33-43, and 48-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Benton et al.* (U.S. Pat. No. 4,876,094) in view of *Wong et al.* (U.S. Pat. No. 6,120,803).

In particular, the Official Action states the following:

> The instant invention is drawn to an oral solid active compound unit comprising a microsphere, the microsphere comprising: a matrix comprising a mixture of at least one fatty alcohol and at least one solid paraffin; and an acid-labile active compound, selected from the group consisting of an acid-labile proton pump inhibitor, a salt of an acid-labile proton pump inhibitor with a base, and a hydrate of a salt of an acid-labile proton pump inhibitor with a base, wherein said acid-labile active compound is present in said matrix. The instant invention is also drawn to an oral solid active compound unit comprising a microsphere, the microsphere comprising: a matrix comprising a mixture of at least one fatty acid ester or at least one triglyceride, and at least one solid paraffin; and an acid-labile active compound, selected from the group consisting of an acid-labile proton pump inhibitor, a salt of an acid-labile proton pump inhibitor with a base, wherein said acid-labile active compound is present in said matrix.

Benton *et al* (`094) teach a dual coated liquid dosage formulation comprising dosage form cores such as matrix beads/microspheres (which can be time release or controlled release devices) containing a therapeutically active compound over which there are applied two unique coatings. These two coatings enable dispersion of the coated dosage form cores in a liquid carrier by imparting stability to the dosage form (see reference column 1, line 55 – col. 2, line 20).

Suitable controlled release type dosage form cores include controlled-release matrix beads/microspheres. The matrix beads/microspheres, typically are formed of a binder which is an insoluble material such *as* a soluble polymer or porous insoluble polymer or a wax which is intimately mixed with the therapeutically active compound (col. 3, lines 8-22).

Ingestible materials useful as a binder include waxes such as paraffin, higher fatty acids, esters of fatty acids such *as* glyceryl tristearate, cetyl palmitate, diglycol stearate, glyceryl myristate, triethylene glycol monostearate, higher fatty alcohols such as cetyl alcohol and stearyl alcohol and high molecular weight polyethylene glycols and mixtures thereof (col. 3, lines 2336). The dosage form cores are microspheres or matrix beads coated with two materials. Most fats or glycerides include minor percentages of sterols, hydrocarbons, tocopherols and other non-glyceride constituents. The fats or glycerides can include mono-, di-, or triglycerides (col. 3, line 67 – col. 4, line 14). The binder can comprise *as* little as 5 or 10% of the core to better than 90% of the core (col. 3, lines 37-46). These amounts read on the amounts of fatty alcohol and solid paraffin claimed by Applicant in claims 54-60. Moreover, with regards to amounts, the Examiner notes that generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In this instance, prior art teaches a similar formulation comprising similar amounts of fatty alcohols, fatty acid esters, waxes and the like.

Alternative to a homogenous mixture, a matrix bead/microsphere can be a core mixture of larger fragments of therapeutically active compound together with binder. In another variation, the binder can envelop a fragment of therapeutically active substance forming a microsphere, which is essentially a microcapsule. Assorted and various matrix bead and microsphere configurations are suitable provided they do not substantially exceed 1400 micron diameter (col. 3, lines 47-59).

The dual coated microspheres/matrix beads are preferred dosage forms and have a size range of 15-300 microns (col. 5, lines 48-54). This range meets Applicant's claimed range of 50-500 microns. The controlled release microspheres/matrix beads can be prepared by microencapsulation processes including prilling, pan coating, granulation fluidization processes and other processes (col. 5, lines 60-66).

Therapeutically active ingredients are taught at column 6, lines 41-50. Active ingredients taught include theophylline, antihistamines, cold formulations, analgesics, amino acid supplements, vitamins (i.e., vitamin C), geriatric drugs, antidepressants and the like.

Benton *et al.* teach liquid dosage formulations. Benton *et al.* do not teach solid formulations and do not teach an active compound being an acid-labile proton pump inhibitor or a salt of an acid-labile proton pump inhibitor with a base or a hydrate of a salt of an acid-labile proton pump inhibitor with a base.

Wong *et al.* (`803) teach a prolonged release active agent solid dosage formulation adapted for gastric retention. The dosage formulation includes coated microspheres of an active agent or microspheres of an active agent and adjuvant, wherein especially suitable active agent are active agents for the localized treatment of gastric acidity and gastrointestinal disorders (i.e., duodenal/peptic ulcers; chronic gastritis) such as omeprazole and lansoprazole (see reference column 18, line 1 – col. 20, line 12). Additional active agents include proteins, steroids, antidepressants, analgesics, antihistamines and the like.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the proton pump inhibiting active compounds, such as omeprazole or lansoprazole taught by Wong *et al.* within the dosage formulation of Benton *et al.,* because Wong *et al.* teach that the active agents (i.e., omeprazole, lansoprazole) are especially useful in their invention for the localized treatment of gastric acidity and gastrointestinal disorders, such as duodenal ulcers, peptic ulcers and chronic gastritis. The expected result would be an improved and effective proton pump inhibiting dosage formulation for the treatment of gastrointestinal disorders and conditions.

RESPONSE

Applicants respectfully traverse this rejection of presently pending claims 11-15, 18-20, 33-43, and 50-60. Applicants further point out to the Examiner that claims 48 and 49

have been cancelled.

The reference of record does not teach or suggest applicants' inventive subject matter as a whole as recited in the claims. Applicants assert that the cited reference fails to establish a *prima facie* case of obviousness against the presently pending claims.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference. *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

However, solely to remove the grounds for the present rejection, and to obtain a Notice of Allowance, applicants have amended claims 11, 12, and 18 to recite "wherein the microsphere does not comprise an enteric coating." Support for this amendment may be found on page 3 of the specification in the first paragraph of the Description of the Invention. In particular, the last sentence of this paragraph states that "the acid-labile active compound does not have to be protected by an enteric coating." Moreover, the last paragraph on page 9 of the instant application discloses that no gastric retention of the administration form is to be expected. Specifically, the instant application discloses "owing to the narrow monomodal particle spectrum and a uniform, spherical form of the microspheres thus obtained, a uniformly smooth surface, a uniform, defined delivery of

active compound and, with respect to the gastric passage in the case of oral administration forms (determined by the small particles), behavior like that of a solution is to be expected."

Further, applicants believe that there is no suggestion or motivation supporting the combination of *Benton et al.* with *Wong et al.* A skilled artisan would not have been motivated to combine a liquid dosage formulation for release in the intestines with a solid formulation for release in the stomach to create the instant invention which recites a solid administration form for release in the intestines.

Specifically, *Benton et al.* are concerned with stability of an active agent in an acidic environment. *Benton et al.* provide a dual-coated microsphere in a sugar-based acidic liquid carrier to achieve stability by preventing release of the active component. In particular, *Benton et al.* discloses a liquid controlled release dosage formulation. In contrast, *Wong et al.* are concerned with retaining a controlled release solid dosage form in the stomach so as to prolong delivery of an active component in the acidic environment of the stomach.

Particularly, the skilled artisan reviewing the *Wong et al.* reference would not find it obvious to combine *Wong* et al. with *Benton et al.* because *Wong et al* .teaches away from *Benton et al. Wong et al.* disclose a physical form which is designed to have prolonged release in the stomach. *Wong et al.* disclose, at col. 1, lines 34-38, that to provide a desired therapeutic effect for active agents that are not easily absorbed by the small intestine or that do not dissolve readily, the window for active agent absorption in the small intestine may be too short. The *Wong et al.* reference discloses that "active agents useful in this invention include" omeprazole and lansoprazole at col. 18, line 18 – col. 20, line 12. Therefore, the *Wong et al.* reference teaches away from releasing active labile ingredients

such as active labile proton pump inhibitors in the intestines. A skilled artisan would have no motivation to combine *Wong et al.* with *Benton et al.* which dosage form addresses release in the intestines.

Further, in view of applicants' amendment such that no enteric coating is needed, the instant invention is even further distinguished from those of *Benton et al.* and *Wong et al. Benton et al.* disclose a coat which is "amenable to being rendered permeable in early portions of the gastrointestinal tract." Col. 4, lines 33-34. In contrast, *Wong et al.* are concerned with retaining a controlled release solid dosage form in the stomach so as to prolong delivery of an active component in the acidic environment of the stomach. Therefore, a skilled artesian would not have been motivated to combine a liquid administration form with enteric coating for release in the intestines with a solid administration form comprising a proton-pump inhibitor for release in the stomach to create the instant invention of a solid administration form comprising a proton pump inhibitor without an enteric coating for release in the intestines.

In view of the foregoing, it is submitted that claims 11-15, 18-20, 33-43, and 50-60 are patentable over the applied references. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

2. Rejection of claim 44 under 35 U.S.C. §103(a)

The Official Action states that claim 44 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Benton et al.* (U.S. Pat. No. 4,876,094) in view of *Wong et al.* (U.S. Pat. No. 6,120,803) as applied to claims 11-15, 18-20, 33-43 and 48-60 above and further in view of *Steber* (U.S. Pat. No. 5,213,810).

In particular, the Official Action states the following:

The teachings of Benton *et al.* and Wong et al. are delineated above. Benton *et al.* teach paraffin (col. 3, line 27). Benton *et al.* do not teach the paraffin, ozocerite.

Steber ('810) teaches stable microsphere compositions and methods of making microsphere compositions containing a fat, wax or mixture thereof; a biologically active protein, peptide or polypeptide; and an oil, semi-soft fat, fatty acid derivative or mixture thereof (see Abstract and Claims). Suitable natural waxes taught include fossil or earth waxes such as ozocerite and petroleum waxes such as paraffin, microcrystalline (col. 2, lines 60-68).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the particular wax, ozocerite of Steber within the dosage formulations of Benton *et al.* One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success because Steber teach that suitable and effective waxes used in their microsphere compositions include naturally derived waxes of fossil or earth waxes, such as ozocerite. The expected result would be an improved and beneficial proton pump inhibiting dosage formulation for treating an array of gastrointestinal disorders.

RESPONSE

Applicants respectfully traverse the rejection of presently pending claim 44. For the same reasons as defined above, the references of record do not teach or suggest applicants' inventive subject matter as a whole as recited in the claims. The addition of *Steber* does not remedy the deficiencies of *Benton et al.* and *Wong et al.*

Steber does not address the deficiency of *Benton et al.* and Wong *et al.* of acid labile compounds being released in the intestines. *Steber* only addresses parenteral administration. The disclosure of a parenteral administration method would not help teach or suggest applicants' inventive subject matter of an oral administration form of an acid labile active for administration in the intestines which does not require an enteric coating. Therefore, the addition of *Steber* does not address the deficiency in the rejection to independent claim 11 to which claim 44 depends, and does not render obvious claim 44.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection to claim 44.

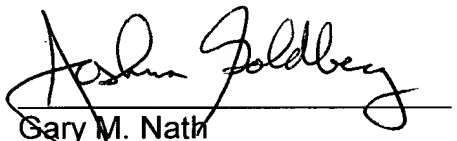
CONCLUSION

It is submitted that the presently claimed subject matter is novel and patentably distinguishable over the prior art of record. Favorable action with an early allowance of pending claims 11-15, 18-20, 33-44 and 50-60 is earnestly solicited.

The Examiner is welcomed to telephone the undersigned attorney if she has any questions or comments.

In the event that this paper is not timely filed, Applicants hereby petition for an appropriate extension of time. Please charge any such extension of time fee, any fee deficiency or credit any overpayment to deposit account no. 14-0112.

Respectfully submitted,
NATH & ASSOCIATES PLLC



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